COMMUNICATION

# Synthesis of highly functionalised, optically active disaccharide receptors by sequential aryl–alkyne cross- and oxidative acetylenic homo-coupling

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***Received (in Cambridge, UK) 22nd September 2000, Accepted 26th October 2000***
***First published as an Advance Article on the web 10th November 2000***

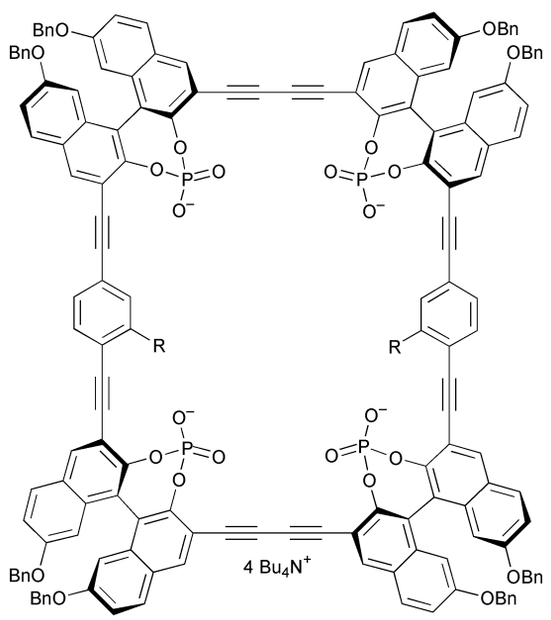
**The synthesis of novel 1,1′-binaphthalene-derived cyclophanes with a rectangular cavity lined by convergent phosphate and carboxy residues for complexation of disaccharides in protic solvent mixtures is described.**

Molecular recognition of carbohydrates is a critical event in a wide range of biological phenomena and the first step in numerous processes based on cell–cell interactions, including the transmission of diseases and the operation of the immune system.[1] The structural factors of protein–carbohydrate complexation have been displayed in a large number of X-ray crystal structures.[2] Nevertheless, important open questions remain concerning the contribution of individual bonding interactions to selective recognition and, in particular, the role of apolar association and hydrophobic desolvation.[3] In recent years, studies with artificial receptors[4] started complementing biological investigations in the search for a molecular-level understanding of the principles governing carbohydrate recognition. Such receptors could ultimately become interesting novel therapeutic agents, potentially serving as antiadhesive drugs,[1b] or become templates for oligosaccharide synthesis.

We previously reported the complexation ability of the 1,1′-binaphthalene-derived, optically active cyclophane (*R*,*R*,*R*,*R*)-**1**.[5] In protic solvent mixtures, this tetraanionic receptor selectively forms stable 1 : 1 complexes with disaccharides. Ionic H-bonding between the four phosphate residues in the receptor and the HO-groups of the substrates was presumed to be the major host–guest interaction in these complexes. Here, we describe the synthesis of the novel, optically active cyclophanes (*R*,*R*,*R*,*R*)-**2** and (*R*,*R*,*R*,*R*)-**3** featuring two additional carboxy recognition sites. A strong motivation for the introduction of two carboxylate residues in (*R*,*R*,*R*,*R*)-**3** was the desire to potentially mimic, in a suitable pH-range, the catalytic function of the corresponding residues in the active site of glycosidases.[6] Therefore, the synthesis of this cyclophane was considered a first step towards a template for catalytic disaccharide cleavage.

For the assembly of the highly functionalised receptors, a novel synthetic route was conceived which elegantly takes advantage of [Pd]-catalysed aryl–alkyne cross-[7] and oxidative acetylenic homo-coupling[8] methodology (Scheme 1). Bis-silyl-protected 1,1′-binaphthalene (*R*)-**4**[9] was monodeprotected to give (*R*)-**5**, which was cross-coupled[7,10] with methyl 2-(3,3-diethyltriaz-1-enyl)-5-iodobenzoate[11] to yield methyl ester (*R*)-**6**. Treatment with methyl iodide gave (*R*)-**7**,[12] which was protodesilylated to provide (*R*)-**8**, and subsequent Glaser–Hay homo-coupling[8,13] led to dimeric (*R*,*R*)-**9**.

For the synthesis of the open-chain tetrameric precursor (*R*,*R*,*R*,*R*)-**10**, dimeric diiodo derivative (*R*,*R*)-**9** was doubly cross-coupled[7,10] with monomeric (*R*)-**5**. Slow addition of an excess of (*R*)-**5** to a solution of (*R*,*R*)-**9** and active catalyst produced predominantly tetrameric (*R*,*R*,*R*,*R*)-**10**, together with by-product resulting from competing oxidative dimerisation of (*R*)-**5**. Protodesilylation of (*R*,*R*,*R*,*R*)-**10** led to terminally bis-deprotected (*R*,*R*,*R*,*R*)-**11**, and subsequent intramolecular

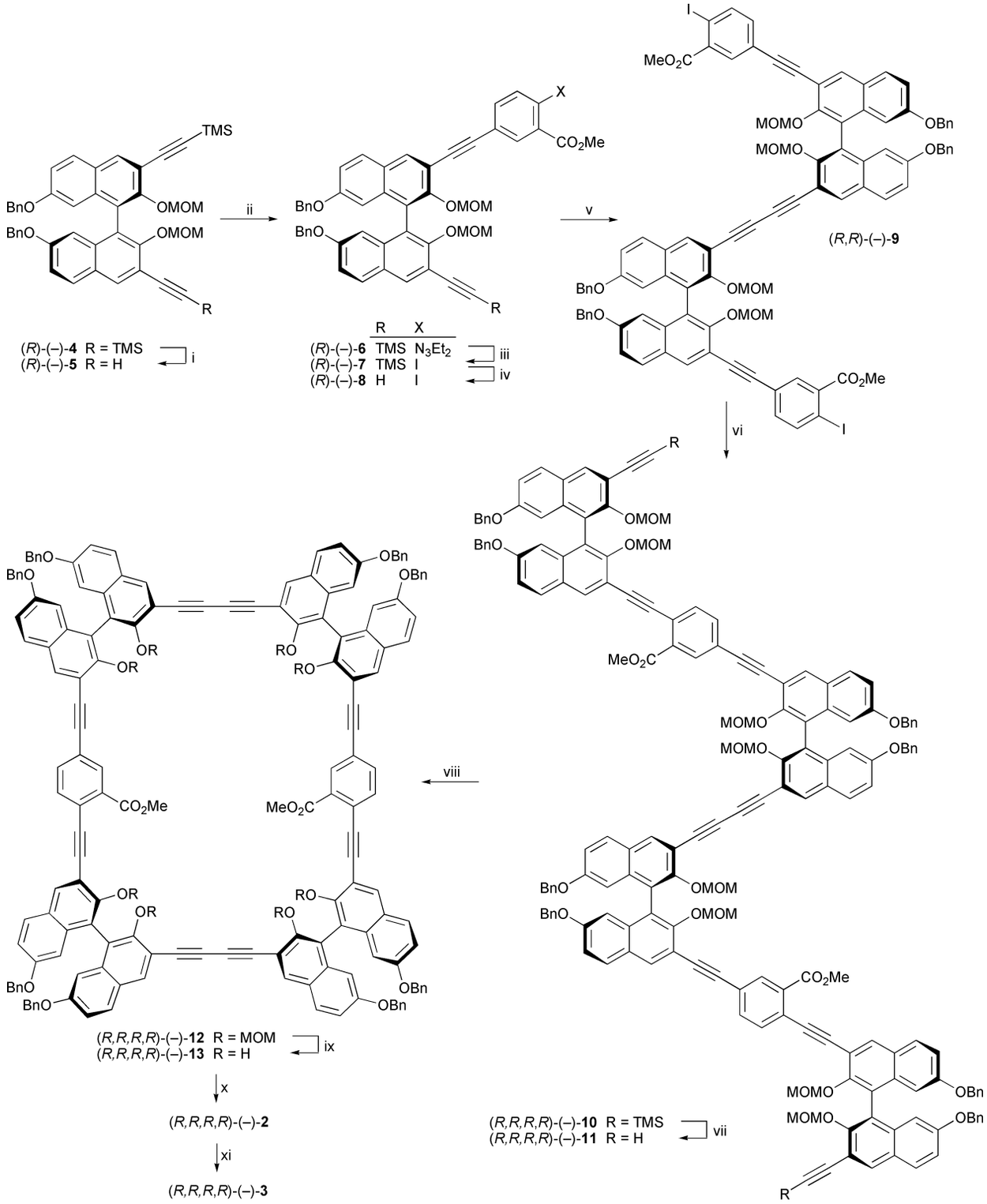



(*R*,*R*,*R*,*R*)-(–)-**1** R = H
(*R*,*R*,*R*,*R*)-(–)-**2** R = $CO_2Me$
(*R*,*R*,*R*,*R*)-(–)-**3** R = $CO_2^-$ $K^+$

Glaser–Hay coupling[8,13] under high dilution furnished the 48-membered macrocycle (*R*,*R*,*R*,*R*)-**12**, besides some starting material and higher oligomers. Preparative size-exclusion chromatography (NovoGROM GPC 1000 column, 10 μm; eluent: PhMe) gave pure cyclophane (*R*,*R*,*R*,*R*)-**12** in excellent 77% yield.† MOM ether hydrolysis under very dilute acidic conditions,[14] hence avoiding subsequent naphtho[*b*]furan formation, afforded compound (*R*,*R*,*R*,*R*)-**13** with eight convergent HO-groups. Subsequent treatment with phosphorus oxychloride, followed by hydrolysis and counter-ion exchange, gave the targeted tetraphosphate receptor (*R*,*R*,*R*,*R*)-**2**. Methyl ester cleavage under anhydrous basic conditions[15] afforded dicarboxylate receptor (*R*,*R*,*R*,*R*)-**3**. Evidence for its hexa-anionic structure was provided by negative electrospray ionisation (NESI) mass spectrometry, which showed dianionic and trianionic ionised species.‡

Complexation of disaccharides **14**[16] and **15**[17] with receptor (*R*,*R*,*R*,*R*)-**2** was investigated by $^1$H-NMR titrations in $CD_3OD$–$CD_3CN$ mixtures. Resonances corresponding to the anomeric protons H-C(1) shifted upfield upon addition of the host (Table 1). Tetraphosphate (*R*,*R*,*R*,*R*)-**2** exhibited a high affinity[18] for both disaccharides in the competitive solvent mixture $CD_3OD$–$CD_3CN$ 20 : 80 (*v*/*v*). Whereas no discrimination between both substrates was observed, the selectivity over the smaller octyl β-D-glucopyranoside (**16**) was very large since no binding of the latter could be detected. The association free energy measured for the complex (*R*,*R*,*R*,*R*)-**2**·**14** in $CD_3OD$–

 DOI: 10.1039/b007706m




**Scheme 1** Synthesis of receptors (*R*,*R*,*R*,*R*)-**2** and (*R*,*R*,*R*,*R*)-**3**. *Reagents and conditions*: i, $Na_2B_4O_7 \cdot 10\ H_2O$, THF, $H_2O$, 20 °C, 31% (98% based on reacted (*R*)-**4**); ii, methyl 2-(3,3-diethyltriaz-1-enyl)-5-iodobenzoate, [$PdCl_2$(dppf)], CuI, $HNEt_2$, 40 °C; then (*R*)-**5**, PhMe, 76%; iii, MeI, 130 °C, 99%; iv, $K_2CO_3$, THF, MeOH, 20 °C, 93%; v, CuCl, $O_2$, TMEDA, $CH_2Cl_2$, 20 °C, 99%; vi, [$PdCl_2$(dppf)], CuI, $HNEt_2$, PhMe, 35 °C; then (*R*)-**5**, 61%; vii, $K_2CO_3$, THF, MeOH, 20 °C, 99%; viii, CuCl, dry air, TMEDA, $CH_2Cl_2$, *c* $0.35 \times 10^{-3}$ mol $l^{-1}$, 25 °C, 77%; ix, conc. HCl, MeOH, THF, 20 °C, 95%; x, $POCl_3$, $NEt_3$, $CH_2Cl_2$, 20 °C; then THF, $H_2O$, 40 °C; then Dowex® ($Bu_4N^+$), $CHCl_3$–MeCN 1 : 1, 86%; xi, KOTMS, THF, 20 °C, 96%; dppf, 1,1′-bis(diphenylphosphino)ferrocene.

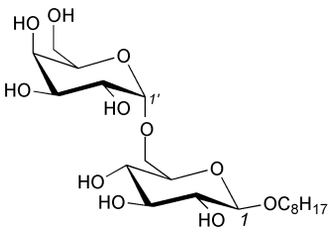
$CD_3CN$ 12 : 88 (*v*/*v*) was significantly higher than that determined for the analogous cyclophane (*R*,*R*,*R*,*R*)-**1** lacking the two methyl carboxylate groups ($-\Delta G^\circ = 26.4$ *vs.* 23.4 kJ $mol^{-1}$).[5] These two extra sites presumably enhance binding affinity both by direct H-bonding interactions with the sugar substrate as well as by providing an overall tighter host–guest fit.

In preliminary studies, substantial upfield shifts ($-\Delta\delta > 0.06$ ppm) of the resonances corresponding to the anomeric proton H-C(1) of **14** and **15** upon addition of cyclophane (*R*,*R*,*R*,*R*)-**3** have been measured by $^1$H-NMR spectroscopy in $CD_3CN$ solutions containing up to 40% (*v*/*v*) of $CD_3OD$. However, quantitative interpretation of the disaccharide-recognition ability of this hexaanionic host by fitting NMR titration data to a simple 1 : 1 association model failed so far and additional solvent-dependent study will be required. Also, delicate investigations to demonstrate the potential of (*R*,*R*,*R*,*R*)-**3** as a macrocylic template for catalytic disaccharide hydrolysis are now being pursued.

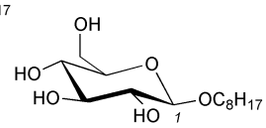
**Table 1** Association constants $K_a$ and complexation free energies $\Delta G^\circ$ from 500 MHz $^1$H-NMR binding titrations for 1 : 1 complexes of saccharides with receptor (*R*,*R*,*R*,*R*)-**2** at 300 K. Also shown are the complexation-induced changes in chemical shift of the anomeric protons H–C(1) at saturation binding ($\Delta\delta_{sat}$) and the degree of saturation reached

| Substrate[a] | Solvent $CD_3OD$–$CD_3CN$ (*v*/*v*) | $K_a$[b]/1 mol$^{-1}$ | $-\Delta G^\circ$/ kJ mol$^{-1}$ | $\Delta\delta_{sat}$[b,c] (ppm) | Degree of saturation (%) |
|---|---|---|---|---|---|
| **14** | 12 : 88 | 41 000 | 26.4 | −0.09 | 93 |
| **14** | 20 : 80 | 21 700 | 24.7 | −0.05 | 81 |
| **15** | 20 : 80 | 20 800 | 24.7 | −0.02 | 90 |
| **16** | 20 : 80 | no binding | | | |

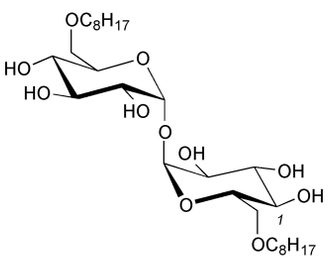
[a] The substrate concentration was held constant at *ca.* 0.25 $10^{-3}$ mol l$^{-1}$ and the receptor concentration varied between 0.04 $10^{-3}$ and 0.60 $10^{-3}$ mol l$^{-1}$. [b] The association constants and complexation-induced changes in chemical shift at saturation binding were obtained by non-linear least-squares curve fitting of the titration data. The reproducibility of the $K_a$ values was ±20% in duplicate and triplicate runs. 1 : 1 Host–guest complexation stoichiometry was confirmed by Job plot analysis. [c] The negative sign designates an upfield shift.




Octyl β-D-melibioside **14**




Octyl β-D-glucopyranoside **16**




6,6'-Bis-*O*-octyl-α,α-trehalose **15**

## Acknowledgements

Support by the Swiss National Science Foundation and by doctoral fellowships from the *Stipendienfonds der Basler Chemischen Industrie* and from *Novartis AG* (A. S. D.) is gratefully acknowledged.

## Notes and references

† *Selected data* for (*R*,*R*,*R*,*R*)-**12**. $[\alpha]_D^{20}$ −570.8 (*c* 0.50 in $CHCl_3$); CD $\lambda_{max}$ ($CHCl_3$)/nm 260 ($\Delta\varepsilon$/l mol$^{-1}$ cm$^{-1}$ +130), 270 (+125), 302 (+205), 329 (−70), 383 (−260); $\delta_H$(500 MHz, $CDCl_3$, 300 K) 2.50, 2.58, 2.67 and 2.69 (24 H, 4 s), 4.00 (6 H, s), 4.62–4.73 (16 H, m), 4.82–5.04 (16 H, m), 6.45–6.46 (8 H, m), 7.05–7.21 (48 H, m), 7.62–7.63 (4 H, m), 7.74, 7.75, 7.78 and 7.79, (8 H, 4 d, *J* 9.1), 8.169–8.174 (2 H, m), 8.125, 8.133 and 8.19 (8 H, 3 s); *m*/*z* (MALDI-TOF) 2822.3 ([M + Na]$^+$, ($^{13}C_2{}^{12}C_{182}H_{140}O_{28}Na$)$^+$ requires 2821.9, 100%).

‡ *Selected data* for (*R*,*R*,*R*,*R*)-**3**. $\delta_P$(121.5 MHz, $(CD_3)_2SO$, 300 K) 4.87; $\delta_H$(500 MHz, $(CD_3)_2SO$, 394 K) 0.94 (48 H, t, *J* 7.4), 1.32–1.39 (32 H, m), 1.59–1.65 (32 H, m), 3.18 (32 H, t, *J* 8.3), 4.74–4.91 (16 H, m), 6.58–6.82 (8 H, m), 7.06–7.60 (52 H, m), 7.88–7.96 (8 H, m), 8.03, 8.17 and 8.25 (8 H, 3 s), 8.19–8.27 (2 H, m); *m*/*z* (NESI) 1390 ([M − 4 $NBu_4$ + Na + $H_3O$]$^{2-}$, $\frac{1}{2}$($^{13}C_2{}^{12}C_{164}H_{97}O_{29}P_4K_2Na$) requires 1390.2, 57%), 1370 ([M − 4 $NBu_4$ + 2 H]$^{2-}$, $\frac{1}{2}$($^{13}C_2{}^{12}C_{164}H_{96}O_{28}P_4K_2$) requires 1370.2, 64%); 920 ([M − 4 $NBu_4$ + Na]$^{3-}$, $\frac{1}{3}$($^{13}C_2{}^{12}C_{164}H_{94}O_{28}P_4K_2Na$) requires 920.5, 57%), 913 ([M − 4 $NBu_4$ + H]$^{3-}$, $\frac{1}{3}$($^{13}C_2{}^{12}C_{164}H_{95}O_{28}P_4K_2$) requires 913.1, 100%).

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